The Breast and Colon Cancer Family Registries (CFRs)

www.epi.grants.cancer.gov/CFR/

Background

The etiology of breast and colon cancer is complex, involving sophisticated interplays of genetic and environmental factors. Genetic risk may be due to mutations of high-risk/low frequency genes as well as common polymorphic variants in metabolic pathways. Environmental and lifestyle factors, such as exogenous and endogenous hormonal exposure, ionizing radiation, diet, and physical activity, affect cancer risk as well.

Recent progress notwithstanding, genetic epidemiology studies of breast and colon cancer must still address questions ranging from the identification and characterization of new susceptibility genes to the evaluation of genetic and environmental modifiers of risk and their interactions, to the application of these findings to cancer prevention and control.

What is the best way to study these issues? Increasing statistical power requirements and the need for complementary designs are now requiring large populations and complementary modes of ascertainment. Population-based case families are important to determine penetrance and prevalence of susceptibility genes in the population and to guide public health interventions. Ethnically or geographically isolated populations bearing founder or ancestral mutations of cancer susceptibility genes (i.e., Ashkenazi Jewish) are useful for characterizing specific mutations and their impact on communities. Population-based cases as well as their relatives and unrelated controls are important for assessing the effect of common polymorphisms.

To address these needs, the international Breast and Colon Cancer Family Registries (CFRs) have developed a unique and flexible research infrastructure to support interdisciplinary research in the genetic epidemiology of cancer and to identify and characterize susceptible populations for preventive interventions and clinical trials.

The CFRs Design

Ascertainment is dual, through population-based registries and high-risk cancer clinics. Complete family history of cancer data are collected from probands and validated. Standardized Epidemiology, Diet and Treatment questionnaires are sent to all probands and relatives. Proxy questionnaires are collected from next of kin for deceased individuals. Cancer diagnosis is confirmed through medical records and pathology reports. Biospecimens (blood, lymphocytes, plasma, mouthwash, paraffin blocks and, for a subset of participants, fresh-frozen tissue) are collected, processed, and stored in semicentralized repositories. EBV-transformed cells are established for selected individuals/families. Mutational analysis for BRCA1, BRCA2, A-T, CHEK 2, MSH2 and MLH1, and other candidate breast and colon cancer susceptibility genes as well as microsatellite instability (MSI) assessment of all colon tumors are in progress (Figure 1).

The NCI's Informatics Center's Central Database collects and manages all of the anonymized CFRs data as well as data from ancillary and pilot studies. External Advisory Committees provide scientific review for collaborative research proposals submitted by investigators from the CFRs and from the research community at large, and provide advice on research issues.

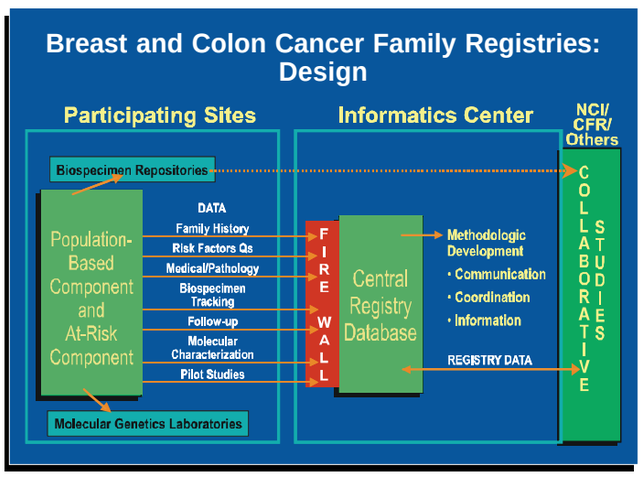

Figure 1.

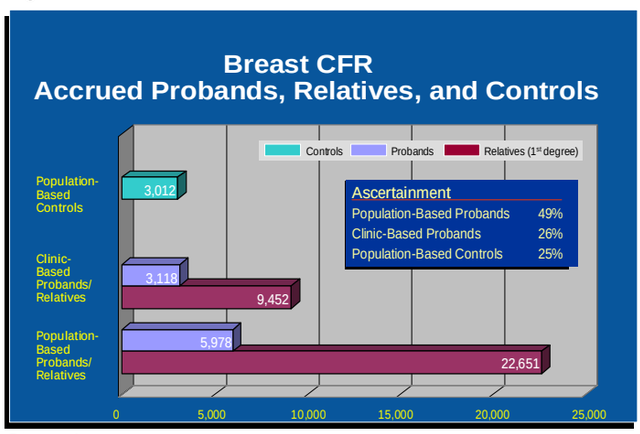

Chart 1.

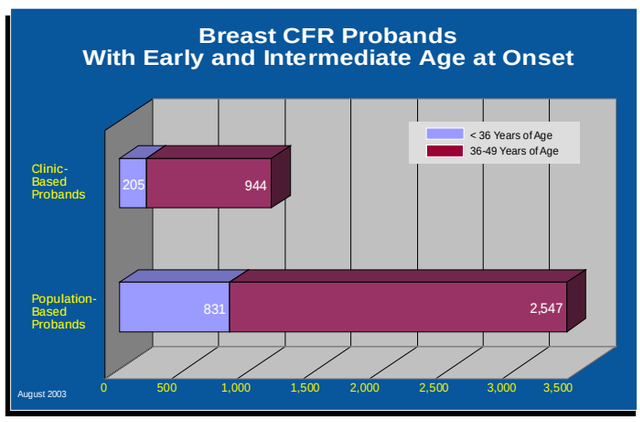

Chart 2.

Current Status of the CFRs

A. Breast CFRs (since 1997)

Probands/Families recruitment (each proband represents a family): as of July 2003, the Breast CFR recruited a total of 5,978 population-based families, and 22,651 relatives have consented from these families. Similarly, 3,118 clinic-based families have been recruited, and 9,452 of the existing relatives have consented. There are 3,012 population-based controls, and their family histories also have been collected, as shown in Chart 1.

Cases with young age at onset are a particularly interesting category to examine for genetic determinants of breast and ovarian cancer. Chart 2 shows the current accrual for probands under 50 years of age by ascertainment and age at onset.

As part of the current mutational analysis plan, 6,817 individuals have been tested for BRCA1 and 5,935 for BRCA2 with a variety of techniques showing 80–100% sensitivity and 100% specificity for detection of protein truncating mutations (Andrulis et al., 2002). This includes probands and the families of positive probands. So far, 959 carriers of deleterious mutations in either of the two genes have been identified, as shown in Chart 3.

Following the discovery of the Ashkenazi founder mutations, four of the Breast CFR participating institutions have specifically targeted recruitment of Ashkenazi families and controls. The unique collection of well-characterized Ash-kenazi families represent 21% of total Breast CFR recruitment. Minority family recruitment, initiated in 1996, will be extended through 2006, specifically targeting African Americans, Hispanics, and Asians. Mutational analysis of known breast cancer susceptibility genes (BRCA 1 and 2, A-T, CHEK 2) is in progress.

B. Colon CFRs (since 1999)

Proband/Families recruitment (each proband represents a family): as of July 2003, the Colon CFR recruited a total of 5,194 population-based families, and 21,629 relatives have consented from these families. Similarly, 597 clinic-based families have been recruited, and 5,316 of the existing relatives have consented. There are 3,000 population-based controls, and their family histories also have been collected, as shown in Chart 1a.

Of the proband cases with ascertained age at onset, 1,492 were <50 years of age at onset and 4,098 were ≥50 years of age at onset, as shown in Chart 2a, by ascertainment.

Minority family recruitment, initiated in 1999, will be extended to target specifically African Americans and Japanese Americans, two populations showing increasing incidence rates of colon cancer.

As part of the current MSI assessment, 3,622 tumors have been tested with a standard markers panel. Of these, 568 have been classified as MSI H (defined as positive for more then 30% of the markers). In addition, immunohistochemistry testing of 2,316 tumors for MLH1 and 2,310 for MSH2 has resulted in, respectively, 328 and 151 negatives, as shown in Chart 3a. Mutational analysis of these two genes for all participants is currently in progress.

Conclusion

Multi-center, interdisciplinary research infrastructures such as the Breast and Colon CFRs, including both population-based and clinic-based components, may become models to address future population research in cancer genetics and epidemiology. The familial nature of these cohorts, the dual modes of ascertainment, the comprehensive collection of pedigree, epidemiologic, clinical, and molecular data, and the emphasis on special populations (i.e., Ashkenazi Jewish, minorities) allow for maximum flexibility in study design. Therefore, collaborative studies using the Breast and Colon CFRs infrastructure can address a wide spectrum of research questions, ranging from: (a) the identification of new cancer susceptibility genes through linkage and association studies; (b) the characterization of existing cancer susceptibility genes in terms of population allele frequency, penetrance, and genotype-phenotype correlations; and (c) the evaluation of genetics and environmental modifiers of risk.

In addition, the planned further characterization and follow-up of these large familial cohorts will make possible more precise assessment of gene-gene and gene-environment interactions as well as the identification of sub-populations at increased risk for prevention trials and surveillance behavior research.

Information on how to develop and propose collaborative research using the CFRs infrastructure can be found at: ***epi.grants.cancer.gov/CFR***

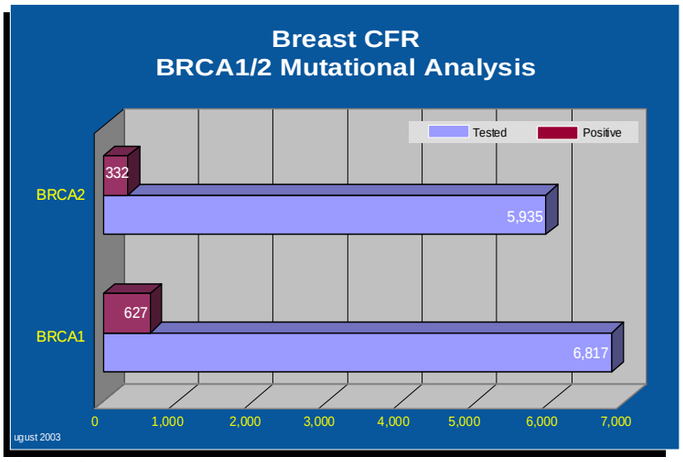

Chart 3.

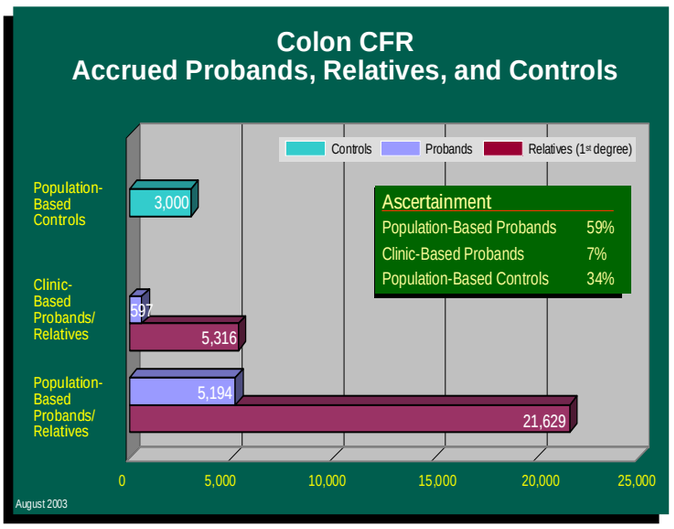

Chart 1a.

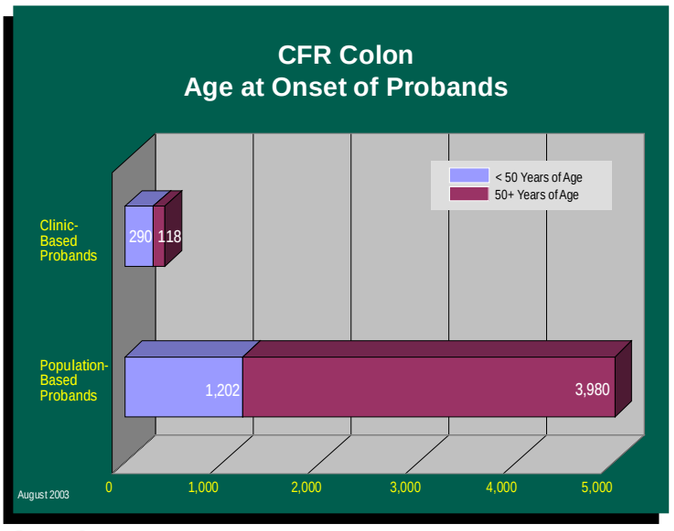

Chart 2a.

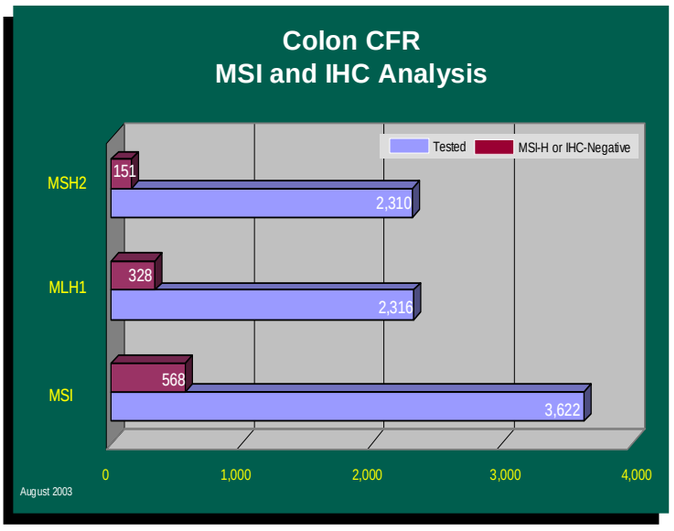

Chart 3a.

To discuss how to submit collaborative proposals, contact: Daniela Seminara, Ph.D., M.P.H., Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, NCI: Phone: (301) 594-7347; E-mail: *seminard@mail.nih.gov*